Peer Review File

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Review Comments

1. English language of this paper needs substantial editing after extensive revisions.
Reply: The manuscript has been polished by a professional polish agency (AJE)

Changes in the text: We revised the manuscript using the "Track Changes" function

2. Abstract. In the background part, it remains unclear why there is a need for a new N staging and the term "seem to confer" is vague. Please make it clear. In the methods part, the authors should not use a lot of the space to focus on statistical methods. Please specify the inclusion of subjects, assessment clinical covariates, and survival outcomes. Please also describe how the new N staging was generated. Because there is a lack of external validation of the new N staging, the conclusion should be made with cautions. Further, in the current results, I did not find the supporting findings for similar prognostic value between LNM and TDs.

Reply: We appreciate the comments and we have modified our text as advised. See page 1 line 17-22; page 1-2; line 25-31; page 2, line 45-48.

Changes in the text: 1) However, the prognostic value of TDs when concomitant with LNM for rectal cancer after neoadjuvant chemoradiotherapy (NCRT) remains unclear. This study aimed to evaluate the prognostic value of TDs and when concomitant with LNMs in rectal cancer after NCRT. 2) Data were extracted on the following: age, sex, race, TNM stage, total LNs harvested, positive LNs, histologic type, perineural invasion, grade, carcinoma embryonic antigen status, TD number, and cancer-specific survival (CSS) rates. The primary objective was to determine the prognostic impact of TDs on CSS. The effect of the addition of TD to the LNM count for a novel N stage was also evaluated. 3) The presence of TDs is an independent poor prognostic factor for LARC patients after NCRT. The concomitant presence of TDs and LNM indicates a significantly worse survival, and the addition of TD to LNM may help to better prompt appropriate risk stratification.

3. Introduction. According to line 68-70, there have been a few evidence for the

prognostic roles of TDs. The authors should have comments on these studies, explain why they replicated this, or indicate how their study advance the literature. One rationale for the current research topic is the unclear prognostic value of concomitant TDs and LNM in LARC, but the authors must explain why they need the combination of TDs and LNM in LARC. The authors must explain why a new N staging is needed and please have comments on the limitations of old staging.

Reply: We appreciate the comments and we have modified our text as advised. See page 3-4, line 127-154.

Changes in the text: The prognostic value of TDs may be different from that of treatment-native because of the downstaging effect of NCRT. Some studies have shown that the presence of TDs is associated with a poor treatment response, aggressive clinicopathological features and a poor prognosis in LARC patients after NCRT (10,12,13). A systematic review and meta-analysis including 1,283 patients found that the presence of TDs after NCRT was associated with depth of invasion, lymph node invasion, perineural invasion, synchronous metastasis, and a poor prognosis (10). However, the prognostic value of TDs concomitant with LNM remains controversial for rectal cancer after NCRT for rectal cancer after NCRT. Wang et al. included 550 patients showing that TDs are an independent adverse prognostic factor for LARC after NCRT, particularly for patients with no more than one PLN (14). However, Yu et al. showed that in the current TNM staging system, the classification of TDs in the ypN0 stage was reasonable, while significantly different disease free survival rates were found between the ypN2TD(−) and ypN2TD(+) groups, not for the ypN1group (15). How the prognostic implications of TDs compare with those of LNM remains unclear. This study aimed to evaluate the prognostic value of TDs alone and combined with LNM in LARC patients after NCRT and to reasonably evaluate the addition of TDs to the LNM count.

4. Methodology. Please use a flowchart to indicate the inclusion of eligible subjects. In this part, the authors must have exclusion criteria, detailed descriptions on the assessment of clinical covariates and prognosis outcomes, and follow-up procedures. These are important for a clinical research.
Reply: We appreciate the comments and we have modified our text as advised. See page 4, line 157-170.

Changes in the text: The data were obtained from the Surveillance, Epidemiology and End Results (SEER) 18 (range, 1975–2016) database and analyzed using

SEER*Stat 8.3.8 software. A total of 34,948 patients, according to the 3rd Edition of International Classification of Diseases for Oncology (ICD-O-3) of the rectum (C20.9) who were treated with NCRT between 2010 and 2016, were identified. After the exclusion of patients with a previous cancer diagnosis (N=3265), patients with rectal adenocarcinoma or mucinous or signet-ring cell carcinoma were identified using histology codes (8140-8144, 8210, 8211, 8260-8263, 8440, 8480, 8481, and 8490) (N =31683). Excluded patients included those who did not undergo radical surgical resection (Surg Prim Site code 0-28; N=3856) and those with missing information on tumor deposits (N=15441) and lymph nodes (N=416). After excluding patients for whom the cause-specific death classification was "N/A not first tumor" (N=1120), the survival months flag was not incomplete (N=140), and the T stage was blank (N=987), 9,620 patients were included in the study. In this study, cancer-specific survival (CSS) was defined as death caused by rectal cancer.

5. Statistics. Please indicate P<0.05 is two-sided or not. Please describe how the novel N staging was generated because the authors used "novel". For a new staging, the authors should have a independent dataset to validate its effectiveness. Please explain how to analyze relationships between TDs and demographic and clinicopathological characteristics.

Reply: We appreciate the comments and we have modified our text as advised. See page 5, line 201-202 and 210-211.
Changes in the text: 1) The primary outcome of the study was cancer-specific survival. Patients were divided into 2 groups according to the TD status. 2) We combined the TD count with LNM and proposed a novel N stage with five categories according to the Kaplan-Meier method. 3) A significance level of 0.05 (two-sided test) was applied throughout.